PATENT
Docket No. 532512000500

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Gregory M. LANZA, *et al.*

Serial No.: 09/774,278

Filing Date: 30 January 2001

For: ENHANCED ULTRASOUND DETECTION WITH TEMPERATURE-DEPENDENT CONTRAST AGENTS

Examiner: Shahnam J. Sharareh, Ph.D.

Group Art Unit: 1617

DECLARATION OF GREGORY M. LANZA

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Commissioner for Patents
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I, Gregory M. Lanza, declare as follows:

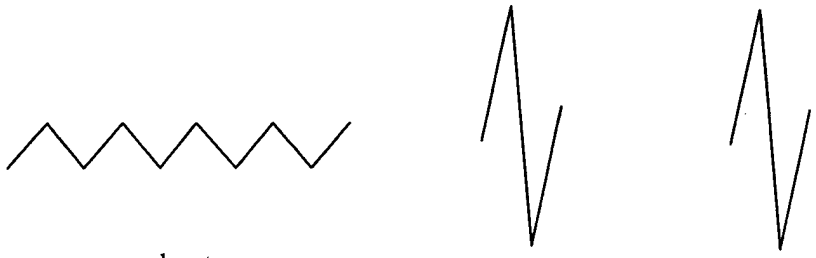
1. I am a co-inventor in the above-referenced case and have been practicing in the area of targeted imaging for over ten years. I have been an inventor or co-inventor in seven issued patents in this area. A copy of my *curriculum vitae* is attached as Exhibit A.

2. I have again reviewed the application and claims in the above-referenced case as well as the Office action mailed 4 June 2003. In this Office action, a rejection is made of all claims based on a combination of four documents; the primary document cited is Unger, U.S. patent 5,149,319. I am familiar with, and have again reviewed, this patent.

3. The disclosure of Unger in '319 does not concern ultrasound imaging. The disclosure of Unger relates to utilizing "hyperthermia potentiators", which may include perfluorocarbon particles, to cause ultrasound to raise the temperature of the tissue surrounding

the perfluorocarbon particles. The purpose of the temperature elevation is to inflict damage on this tissue. There is no disclosure in the Unger '319 patent of actually obtaining any image using ultrasound.

4. The nature of the ultrasound waves that are used by Unger in the '319 disclosure is different from that of those that would or could be used to obtain an ultrasound image. In order to heat the tissue, Unger employs a prolonged, continuous repetition of ultrasound waves (*i.e.*, continuous wave), which waves are of lower frequency than is employed for medical ultrasound imaging. For imaging, investigators transmit a brief, broadband pulse at a frequency of at least 1.5 MHz. A comparison of the type of wave used in each case is illustrated below.



heat

imaging or reflectivity

5. Thus, the ultrasound employed by Unger in the '319 patent is unsuitable for typical medical procedures used in obtaining an image or measuring reflectivity, and may not even be appropriate for Unger's purpose.

6. Example 9 of Unger '319 is a hypothetical study in which rabbits bearing brain VX2 carcinoma are treated with ultrasonic hyperthermia while the tumor temperature and the temperature of the surrounding tissue are monitored. A volume of 3 to 5 cc of perfluorooctylbromide emulsion is injected into a carotid artery immediately upstream of the tumor itself. Rabbits treated with the PFOB emulsion and insonified with 1 MHz show increased tumor temperatures as compared to the surrounding normal tissue.

7. A scientist familiar with this art can not determine whether, in Example 9, the hypothesized increase in temperature at the tumor level is simply an inherent, focused ultrasound effect which is expected to heat tissue, independent of any "potentiators". One would expect that surrounding regions of the brain not directly insonified would be cooler than the tumor. Moreover, the heterogeneous composition of the tumor itself, *e.g.*, fibrotic tissue, calcium deposits, necrosis, would be expected inherently to adsorb and reflect more acoustic energy and than the surrounding normal brain tissue independent of "potentiators". Higher blood flow through the normal brain tissues will dissipate or prevent heat build-up much better than in the tumor, where blood flow is slower and volumes tend to be less than normal. There is ample evidence to suggest that the acoustic energy at 1MHZ reaching the tumor would negligible due to rapid attenuation by intervening tissues. This is why low frequency US (10 to 500 kHz) should have been employed to increase depth of penetration (*i.e.*, depth of penetration is inversely related to frequency).

8. Example 10 is a hypothetical extension of example 9 in which cavitation of gaseous liposomes in the tumor is proposed to increase hyperthermia. Bubbles are high efficient, nonlinear transducers of acoustic energy into mechanical motion, which generate heat [Holt and Roy, *Ultrasound Med Biol.* (2001) 27:1399-1412], so the approach contrasts with the liquid nanoparticles used in the invention.

9. As the Examiner recognizes, Unger '319 does not employ targeted "hyperthermia potentiators." Rather, Unger appears to rely on the positioning of the ultrasound itself to localize the hyperthermia. In the Unger method, is it the temperature of the surrounding tissue that is elevated; in the present invention, such hyperthermia would be undesirable; the temperature

increase is limited as much as possible to the targeted nanoparticles since it is the nanoparticles whose reflectivity is to be enhanced.

10. Our claims are directed to obtaining a reflection – *i.e.*, an image – of a target by enhancing the reflectivity of nanoparticles that are exclusively coupled to the target and not to any surroundings of the target. Unger's methods, even if they included imaging, would be unworkable in the present invention. Nongaseous perfluorocarbon emulsions without targeting are invisible to acoustic imaging and detected only when concentrated at a tissue surface by binding. If there is no targeting to a tissue or organ whose image is desired, there is no way to distinguish that tissue or organ from the surroundings except by its inherent acoustic properties even if ultrasound imaging were employed.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at St. Louis, Missouri, on December 4, 2003.

Gregory M. Lanza